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# BIOLOGICAL BULLETIN

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## THE PROCESS OF REPRODUCTION IN ORGANISMS.

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The present trend of certain lines of biological thought and investigation is toward the conclusion that the process of sexual reproduction in organisms is something unique and associated with a peculiar substance, the germ plasm. This substance is often regarded as self perpetuating, as "continuous" and as independent, except for nutrition, of the organism or soma in which it lives as a sort of parasite and it is the repository of all heritable capacities or characteristics. According to this view the problem of heredity is a problem of the germ plasm and of the germ plasm alone. We are all familiar with the attempts which have been made to interpret the phenomena of asexual reproduction and of regulation with the aid of this hypothesis and the difficulties which these interpretations have encountered are matters of biological history. Moreover, about this hypothesis has grown up a great mass of involved speculation which to many constitutes the foundation of modern biology and which is often accepted as fact rather than hypothesis.

My own lines of investigation and thought have led me to the belief that this germ plasm hypothesis and the subsidiary hypotheses which have grown up about it are not only unnecessary and constitute an impediment to biological thought which has retarded its progress in recent years to a very appreciable extent, but furthermore, that they are not in full accord with observed facts and can be maintained only so long as we ignore the facts. The present paper is an attempt to show that a logical and far more simple theory of reproduction and inheritance is possible on a basis which does not involve so many assumptions of doubtful value and which does agree with the facts of observation.

## I. THE RECONSTITUTION OF ISOLATED PIECES OF ORGANISMS.

If we isolate physically a piece of one of the simpler organisms capable of regulation, *e. g.*, *Hydra*, *Planaria*, we know that within certain limits of size and other conditions the isolated piece reconstitutes itself into a new individual which possesses the essential characteristics of the species. Here then is a case of reproduction induced experimentally.

But what initiates the process of reconstitution? Why does the part become a whole? Most authorities are agreed at present that the isolation of the part is the essential factor in initiation of the process of reconstitution. Before isolation the part in question was in physiological correlation with other parts, *i. e.*, the processes going on in them influenced it in one way or another, affecting the rate, the character, the localization or the sequence of the processes occurring in it. With the act of isolation all these influences cease. What is the result? We see first that the piece or some part of it undergoes a process of dedifferentiation. It may lose to a greater or less extent the structural features which were characteristic of it as a part or it may give rise to embryonic tissue at the cut surface. Sooner or later this process of dedifferentiation is succeeded by a process of redifferentiation and the part gradually becomes a new whole organism.

In this process it is evident, first that the dedifferentiation is the result of the isolation. So long as the piece was in correlation with other parts it remained a part. After isolation it lost the features which characterized it as a part. Secondly, having lost these features to a greater or less extent it began to behave in the manner characteristic of the protoplasm of the species to which it belongs, *i. e.*, it began to develop into a new individual with the specific characteristics. The process of dedifferentiation is not an assumption but an observed fact. It has long been known that in plants many cells are capable of undergoing dedifferentiation. In the lower animals various cells which are certainly not morphologically undifferentiated are capable of becoming embryonic in character and of giving rise, *e. g.*, in regulation, to various parts, and, in nature, to germ cells. These cells are often regarded as indifferent or undifferentiated but I

believe that the facts do not warrant such a designation. The cells are in many cases functional parts of the organism and even their histological characteristics indicate that they are by no means indifferent or reserve cells. Cases in point are the parenchyma of the flat worms and the peritoneal epithelium of polychætes. Apparently in many cases such cells have been called indifferent not because of their embryonic appearance, but because they are capable of forming other parts or of giving rise to germ cells. If we are to hold to the morphological criterion of differentiation then these cells certainly undergo dedifferentiation before they redifferentiate.

The assumption of the existence of accessory germ plasm to account for such cases is entirely unnecessary and superfluous. If protoplasm is a physico-chemical substance why is it necessary to assume the continuous existence of a given specific constitution. Other substances in nature are capable of changing their constitutions in one direction or another under certain conditions, while under others they may return to their original constitution. Some of the most fundamental laws of physics and chemistry are based upon this fact. Moreover, we know that in the metabolic processes of organisms substances may be built up under certain conditions and decomposed under others. What conceivable reason have we for assuming before we have tested all possibilities that these same laws do not hold good for what we are accustomed to call germ plasm?

In short, the evidence of our senses teaches us that in the isolated pieces capable of regulation something identical with or approaching more or less closely to the so-called germ plasm of the species appears *de novo* in consequence of the isolation and that this substance reacts in a definite specific manner essentially similar to the reaction of other isolated masses of the protoplasm of the species. Here then is a case of reproduction for which the assumption of continuity of the germ plasm is purely gratuitous. Whenever in such organisms the conditions which induce differentiation disappear the differentiation disappears to a greater or less degree, in part through the destruction of the more highly differentiated cells and in part through the dedifferentiation of the less highly differentiated cells which are then capable

of undergoing redifferentiation. In other words, the cells which are capable of regulation approach or return to the general type of reaction characteristic of the specific protoplasm.

## II. REJUVENESCENCE IN RECONSTITUTION.

The new whole which arises from the experimentally isolated part may be much smaller than the whole of which it originally formed a part. But the question at once arises, is it younger? Has the process of dedifferentiation carried it back again toward the beginning of the developmental cycle? I have recently shown (Child, '11b) that for *Planaria* this question must be answered in the affirmative and I have further evidence of the same kind for other forms. The new individual resulting from the regulation of a piece is in all respects younger than the animal of which it formed a part. Its rate of metabolism is higher, it is capable of renewed growth and grows at the same rate as a young animal: in every respect it has undergone a process of rejuvenescence. Moreover, the degree of rejuvenescence is in general proportional to the degree of reorganization in the piece, *i. e.*, the degree to which the old structure has disappeared and new structure developed. This process of rejuvenescence involves not only the portions directly concerned in regeneration of lost parts but to a greater or less extent the other portions of the body as well. For example, the removal of the posterior portion of the body of *Planaria* brings about rejuvenescence not only in the posterior region of the piece remaining but in the whole piece, including the head, which plays no direct part in the formation of the new posterior end (Child, '11b).

Rejuvenescence may also be accomplished by starvation followed by feeding, as I showed in the paper referred to, or by any other means which determines the use as a source of energy or the breaking down in any other way of portions of the structural substance of the organism or part. My experiments led me to the conclusion that senescence in its simplest terms consists in a decrease in the rate of metabolism determined by the gradual accumulation of relatively inactive structural obstacles to metabolism, which in turn are the necessary consequence of continued metabolism under constant or relatively constant

conditions and in the presence of nutritive material. If this conclusion is correct then senescence is a necessary feature of life. But senescence in the lower forms does not lead inevitably to death, for any conditions which determine the use as a source of energy or the elimination of a part of these structural substances and so make possible a higher rate of metabolism bring about rejuvenescence. It is perhaps more strictly correct to say that when the formation and deposition of these inactive substances which retard metabolism is more rapid than their break-down and removal then the organism is growing old, but whenever the processes of breaking down and elimination of these accumulations are in excess of the processes which form them the organism is growing young, provided nutrition is available for the increased rate of metabolism which is thus made possible. Sexual reproduction is not the only means by which the organism returns so to speak to or toward the starting point. Every experimental reproduction resulting from the physical isolation of a piece involves necessarily a greater or less degree of rejuvenescence.

We have then in the reconstitution of a part into a new whole after experimental isolation all the essential features of true reproduction and of inheritance. The new individual formed is physiologically and morphologically younger than that from which it originated and it possesses the essential characteristics of the species.

### III. ASEXUAL REPRODUCTION IN NATURE.

In a recent paper (Child, '11a) I have attempted to show that at least many forms of asexual reproduction in nature are essentially similar to the regulatory reconstitution of a piece experimentally isolated. As a matter of fact I believe that all forms of asexual reproduction are of this type. The chief difference between asexual reproduction in nature and the reproduction induced by experimental isolation of pieces is that the isolation in the latter case is physical and complete, while in the former it is usually at first physiological and very often only partial. The simplest types of asexual reproduction which result from autotomy, self-laceration, etc., are identical

in character with the experimental reproductions or regulatory reproductions. Here the reproductive process is initiated by complete physical isolation of a part, either through accident or in consequence of violent stimulation.

In the paper referred to above I have analyzed the concept of physiological isolation and have pointed out the different ways in which it may come about. It is impossible at this time to go into these matters in detail but a brief review of some of the chief points is essential. And first the idea of the physiological dominance and subordination of parts requires attention. Some parts of organisms are relatively dominant physiologically, others relatively subordinate. In the simpler organisms, *e. g.*, the plant, *Tubularia*, *Planaria*, etc., the anterior region or the apical region, the vegetative tip in the plant, the hydranth region in *Tubularia* (Child, '09a, p. 19, '09b), the head region in *Planaria* (Child, '11f) is physiologically dominant over all other parts. The question as to the nature of this dominance will be considered elsewhere.

In such cases reproduction is a relatively simple matter: within certain limits any part of the organism which becomes isolated from the dominant part either physically or physiologically undergoes changes which lead to the formation of a new dominant part, which then controls and determines the reorganization of the remainder of the piece and the result is a new whole. In short, the dominant part represents physiologically the fundamental type of reaction of the specific protoplasm. Some portion, usually the anterior or apical region, of the isolated piece returns to this type of reaction and becomes first of all a new dominant part. In correlation with this subordinate parts then develop so far as material or energy is available.

In the higher organisms conditions may be more complex. The organism may consist of several or many systems, more or less closely correlated and each with its own dominant part. Moreover, as structural characteristics become more stable the capacity for regulation decreases and subordinate parts, even though isolated, may be incapable of any regulation or may give rise merely to new parts like themselves, as for example

in the case of the posterior region of the earthworm, which produces a new posterior end at its anterior end when isolated.

But whatever the complications, the existence of dominant and subordinate parts is of great importance for inheritance. The dominant part can never become anything else for it represents the fundamental reaction system of the species, but from the subordinate parts a new dominant part may arise when they are isolated from their correlation with the old dominant part. In such cases, as I shall show elsewhere, the formation of the new dominant part from the subordinate part is not the restitution of a missing part but the first step in the formation of a new individual from the material of the subordinate part. The old part does not determine that a new head or apical region shall arise, but this occurs in spite of the old part. In general the weaker the old part the more readily does the new head or apical region form and vice versa. The results of my experiments soon to appear demonstrate this beyond a doubt. As regards the formation of a new posterior region from more anterior parts the case is quite different. The posterior region is subordinate to regions anterior to it, consequently the weaker the old part the less readily does the new posterior region arise from it and vice versa. It is possible experimentally to accelerate or even to determine the formation of a new anterior region from a piece by decreasing its rate of metabolism and by the same means to retard or inhibit the formation of a new posterior end.

Secondly, there undoubtedly exists, at least for certain correlative processes a distance-limit, a limit of effectiveness, beyond which the correlative influence is ineffective. Some evidence upon this point I have presented in the paper referred to. This limit of effectiveness is not absolute but varies with the rate of metabolism in the part where the correlative factor originates, with the character of the path of correlation and with other conditions. In various cases we can alter this limit experimentally. On the other hand, the sensitiveness or receptivity of a part to a correlative factor may itself vary according to conditions in and about the part serving as receptor.

From these facts it follows that the physiological isolation of



parts of organisms in nature may occur in various ways: first, increase in size beyond a certain limit may isolate physiologically certain parts from the influence of a dominant part and so lead to reproduction. Second, decrease in the metabolism of a dominant part may decrease the effective distance of the correlative factor and so lead to the physiological isolation of parts without increase in size of the whole. Third, changes in the character of the path of correlation may decrease the distance to which conduction is possible and likewise bring about the physiological isolation of parts. And finally, changes in the receptiveness of subordinate parts may themselves isolate such parts physiologically.

In organisms where the parts in question are capable of regulation such physiological isolation, however brought about, will be followed by a regulatory reconstitution of the isolated part, which may lead either to the formation of a new complete individual, or a new part. The result of the physiological isolation of a part depends upon its degree of differentiation and its regulatory capacity as well as upon the degree and kind of physiological isolation. In my earlier paper examples of the various types of physiological isolation were given and various phenomena of asexual reproduction were analyzed in the light of these ideas.

In many cases the asexual reproductive element appears in a more or less highly differentiated form, *e. g.*, various forms of spores, and in some cases it gives rise to something different from that of which it originally formed a part, as for example in plants, where the spore of the sporophyte gives rise to the gametophyte. Such cases, however, do not in any way conflict with the general conclusion that asexual reproduction is the result of physiological or physical isolation of parts.

If these conclusions are correct, asexual reproduction in nature is essentially similar to the process of reproduction which occurs when we isolate physically a piece of an organism. In the natural process, however, the degree and kind of physiological isolation and the localization of the part isolated are all determined by natural conditions, either internal or environmental.

Moreover, the same considerations apply to the phenomena of

segmentation and reduplication of parts for these are manifestly merely cases of partial reproduction.

In all of these cases physiological isolation is followed by a more or less complete reconstitution, according to the degree and character of the isolation. The result of the physiological isolation is then essentially the same as the result of physical isolation: the isolated part undergoes first a dedifferentiation and loses more or less completely its original characteristics as a part and then redifferentiates into a whole, or in cases of segmentation and reduplication of parts, into a new part. In the cases which are commonly regarded as reproductions the physiological isolation is usually followed sooner or later by complete physical isolation.

We have now to ask the question whether rejuvenescence occurs in asexual reproduction in nature. For certain forms, *e. g.*, *Planaria* (Child, '11b) and some cœlenterates, I have determined experimentally that rejuvenescence does occur in asexual reproduction. As regards the plants there can be no doubt that the same is true: the bud and the new organism arising from the spore both represent conditions nearer the starting point of the developmental cycle than the individuals of which they originally formed a part. If my conclusions stated above concerning the nature of senescence and rejuvenescence are correct there can be no doubt that in every case where a dedifferentiation and redifferentiation follow the physiological isolation of a part a greater or less degree of rejuvenescence occurs.

And finally, there is no more reason to assume the continuous existence of a hypothetical germ plasm in asexual reproduction in nature than in the case where reconstitution follows the experimental physical isolation of a part. After isolation the part may return to or approach the condition of undifferentiated totipotent protoplasm, but the assumption that undifferentiated protoplasm exists in it continuously is wholly gratuitous and superfluous.

#### IV. SEXUAL REPRODUCTION.

We turn now to the problem of sexual reproduction. Here a number of questions require consideration. First, do the gametes arise from an undifferentiated germ plasm which is independent

except for nutrition of the soma or are the gametes physiologically integral parts of the individual? Second, do the gametes before fertilization actually consist of undifferentiated germ plasm or are they differentiated cells like other parts of the organism: in other words are the gametes physiologically young or old cells? Third, why does the egg usually require the special stimulus of fertilization or some artificial stimulus in place of it for the initiation of development? Fourth, why are some eggs naturally parthenogenetic and what is the nature of artificial parthenogenesis? Fifth, how shall we interpret the alternation of generations in plants and metagenesis in animals? Sixth, what is the relation between asexual and sexual reproduction and why is sexual reproduction the only method of reproduction in the higher animals? We shall consider these questions in order.

### 1. *The Origin and Formation of the Gametes.*

The fact that the primitive germ cells can be distinguished very early in development in certain animals, *e. g.*, *Ascaris*, *Cyclops* and various vertebrates, is familiar to all and has commonly been regarded as strong evidence in support of the germ plasm hypothesis. In those cases in which the germ cells do not appear until the adult stage is reached it is of course easy to assume that the germ cells are there throughout development, but are simply not visibly different from other cells during the earlier stages. But is this interpretation the most satisfactory? Does it account for the facts in the simplest way? I believe that it does not.

In the first place all forms in which the germ cells are distinguishable in early cleavage or embryonic stages are forms in which the specifications of the embryonic cells become fixed at an early stage. The germ cells, like other organs, become distinguishable early in the developmental history. The case of *Ascaris*, however, stands to some extent apart from the others, for here the first cleavage separates the egg into two cells, one of which represents the germ cells plus considerable parts of the soma, while the other represents somatic parts alone and undergoes the process known as diminution. The undiminished nucleus is commonly supposed to represent the germ plasm and in this case the hypothesis of continuity seems to be confirmed by observation.

But Boveri's recent work on polyspermic and centrifuged eggs of *Ascaris* (Boveri, '10) throws new light on this case. According to Boveri it is the cytoplasm of the egg that determines which nucleus or nuclei shall undergo diminution and which shall not. All nuclei which come to lie in the animal half of the egg undergo diminution, while those which lie in the vegetative half remain undiminished. If, as most supporters of the germ plasm hypothesis believe, the nuclear substance is the real germ plasm then how shall we account for the fact that here in *Ascaris* it is the cytoplasm that determines which nuclei shall persist as germ plasm and which shall become somatic. The cytoplasm is not properly speaking a part of the germ plasm at all, if we accept the hypothesis in its original form, but rather represents in the egg a differentiated soma, yet if Boveri's conclusion is correct the cytoplasm determines the localization of the germ plasm. Apparently then in this classical case of *Ascaris*, which has been so often quoted as an irrefutable support of the germ plasm hypothesis, the visible distinction between germ cells and soma is determined by cytoplasmic differences along the egg axis. If this is actually the case, the germ plasm is certainly not an independent entity here, but is determined in the same way as many other early embryonic differentiations, *i. e.*, by its environment within the organism.

In *Cyclops* and various other forms the "Keimbahn" is characterized only by certain cytoplasmic granules which do not appear in other cells and by less rapid division. The fact that, at least in some cases these granules originate from nuclei of other cells which have been taken up by the egg, as certain authors have shown, does not alter the case. If the granules are determining factors then the germ plasm is determined by factors in the organism external to it. If they are not determining factors the existence of a "keimbahn" indicates merely that the germ plasm normally arises from a certain part of the organism. These cases then, like that of *Ascaris*, afford no real evidence of the continuous existence of undifferentiated germ plasm.

Investigations of recent years have shown that in at least many cases among the lower vertebrates the primitive germ cells

appear rather early in development and often far from their final position, which they attain by migration. The evidence from observation in these cases also is merely evidence for early differentiation or specification of germ cells, not for continuity of undifferentiated germ plasm. If the germ cells are independent of the soma why should the extensive migrations occur? They behave as if they were physiologically integral parts of the organism, rather than mere parasites upon it, for certainly their migration cannot be regarded as autonomous. Perhaps it should also be pointed out that the evidence for the origin and migration of the primitive germ cells in these forms rests entirely upon the study of fixed material. So far as I am aware, the migrations have not been observed in the living embryos. Does not at least the possibility exist that cells of this character may appear as temporary differentiations or stages in various parts of the embryo, or perhaps that cells with a low rate of metabolism possess these characteristics? But without laying too much weight upon these last suggestions, we are, I think, justified in maintaining that the early appearance of primitive germ cells in vertebrate embryos, when taken as a fact of observation, constitutes evidence for early embryonic differentiation or specification, rather than support for the germ plasm hypothesis.

On the other hand, there is a very large number of forms, both plants and animals, in which the germ cells do not appear until development is completed and then in many cases only periodically. Moreover, in many of these cases they arise from tissues which are visibly differentiated and constitute functional parts of the organism. The coelomic epithelium of the polychætes, for example, is certainly not, if appearances have any significance, an undifferentiated tissue, yet at certain seasons or under certain conditions the germ cells arise from it. It is of course easy to assume that the nuclei of these cells always contain undifferentiated germ plasm, but this is merely forsaking fact for hypothesis.

The parenchyma of the turbellaria and the cestodes is likewise not morphologically an undifferentiated tissue, yet it gives rise to germ cells at a certain stage of development and, if my observations are correct, even the more highly differentiated muscle

cells in certain cestodes may take part in producing germ cells (Child, '06).

In plants buds, which later give rise to germ cells, may arise from parts which have already undergone some degree of differentiation, but which under altered conditions dedifferentiate and produce buds.

How shall we interpret all these and many other facts of the same kind? Shall we conclude that actual observation counts for nothing and that because these apparently differentiated cells produce germ cells they must have contained undifferentiated germ plasm at all times? This is nothing more nor less than an illogical procedure. We are bound to accept our observations until we have some actual evidence which conflicts with them. And not only is there no evidence to prove that cells cannot dedifferentiate and redifferentiate, but there is abundant evidence to prove that many cells can do this. The data upon this point concerning plant cells are numerous and convincing and the occurrence of dedifferentiation has been generally accepted by the botanists as a fact for many years.

In the Protozoa the soma itself or a part of it becomes the gamete. We may of course assume that undifferentiated germ plasm is continuously present in the nucleus or micronucleus, but if this is the case why is not the protozoon always a gamete? Why does sexual reproduction or conjugation in these forms occur only periodically? Evidently it does occur only when the organism is in a certain physiological condition. How are we to account for this fact if the germ plasm is continuously present and independent of the soma?

In both plants and animals the production of gametes is associated with a certain stage of the life history. Even if the primitive germ cells appear in early embryonic life they do not develop into gametes until the growth period is completed. In many plants and some animals it is possible to induce experimentally the development of gametes and the conditions which bring about the sexual stage in these cases are conditions which decrease metabolism and bring the organism into a state physiologically similar to more or less advanced old age. The extensive work of Klebs and others on plants affords the strongest evidence

upon this point. All the facts point to the conclusion that sexual reproduction is a process characteristic of the physiologically old organism. If the germ plasm is continuously present and independent of the soma why should sexual reproduction always be associated with a certain stage of development? Why should it not occur earlier in one individual and later in another? To maintain that the germ plasm cannot obtain sufficient nutrition for its needs until the activity of the soma is on the decline is certainly not in accord with the facts, for even during the growth period the organism may store up reserves, *i. e.*, an excess of nutritive material may be present, but this does not induce sexual reproduction. The assumption of some sort of activation of the sexual organs is merely an assumption of the existence of physiological correlation between the parts concerned and is incompatible with the assumption of independence. On the other hand, we are well aware that, at least in many cases, the gonads when present, influence the metabolism of the soma.

The facts then point almost irresistibly to the conclusion that the formation of gametes is a function of the organism, of the soma, like the formation of leucocytes or any other organ. When the gonads arise early they develop as integral functional parts of the individual and not as parasites. When they arise late or periodically, they arise from parts which have previously been functional parts of the organism and which undergo dedifferentiation and redifferentiation to form gametes in consequence of altered correlative conditions which in turn are associated with advancing senescence.

## 2. *The Differentiation and Physiological Condition of the Gametes.*

It is customary to think of the gametes as consisting of or containing "undifferentiated germ plasm" all ready to develop into a new organism after fertilization. What are the actual facts concerning this point? The primitive germ cell, as a matter of fact is more or less similar in appearance to what we commonly call undifferentiated or embryonic cells, but with the beginning of the growth period the germ cell enters upon a period of differentiation. In the case of the egg this period involves an enormous increase in size and often a very great degree of cytoplasmic differentiation. In most cases also the

nucleus itself becomes differentiated and chromatin disappears from it completely or almost completely. If such a cell as this were found elsewhere in the body and had no reproductive function there is not the slightest doubt that we should regard it as a very highly differentiated and specialized cell.

The spermatozoon is certainly not an undifferentiated cell according to the usual criteria. It is one of the most highly differentiated cells that we know of in the organism. Its differentiation has proceeded along different lines from that of the egg cell, but it is none the less differentiation. Even the chromatin is in a condition different from that in any other cell.

What evidence is there that either of these cells contain "undifferentiated germ plasm?" If we confine ourselves to facts they are among the most highly differentiated cells known.

Morphologically then the gametes are highly differentiated cells. What is their physiological condition? Are they physiologically old or young? As noted above, my experiments with *Planaria* and other forms have led me to the conclusion that senescence consists morphologically in the accumulation of relatively inactive substances or in an increasing density or impermeability or more strictly a decreasing capacity of the colloid membranes to become permeable under stimulation as a necessary result or incident of continued metabolism under relatively constant conditions and in the presence of nutritive material. Usually the inactive substances appear as more or less stable structural features, as differentiations, and their accumulation or increasing density presents increasing obstacles to metabolism. Physiologically then, senescence consists in a decrease in the rate of metabolism in consequence of the increase of structural obstacles to metabolism. The cell becomes less irritable, less capable of stimulation, and if the process goes far enough death or quiescence is the result.

This view of senescence is somewhat different from the theory recently put forward by Minot (Minot, '08). For Minot cytomorphosis, *i. e.*, the increase in cytoplasmic as compared with nuclear material is the important factor in senescence. The two views have, however, much in common, for the accumulation of structural substances usually means increase of cyto-



plasm, but it is possible for a cell or an organism to grow old without any such increase in bulk of the cytoplasm, merely in consequence of the increase in density and impermeability of its membranes, or in consequence of loss of water.

Moreover, I am unable to accept Minot's conclusion that no cells except the egg undergo rejuvenescence. I have pointed out above that rejuvenescence undoubtedly occurs in many somatic cells in the lower organisms and I believe the same is true, at least for certain cells, even in mammals. In gland cells for example, the loading of the cell seems to me to represent in all respects a period of senescence, ending in almost complete quiescence. With the beginning of the discharge of the accumulated material rejuvenescence begins and at the end of this period the cell is both morphologically and physiologically young, though not necessarily embryonic, that is to say, the process of rejuvenescence which it has undergone does not necessarily result in the disappearance of its characteristics as a gland cell, but it has undoubtedly become a young gland cell.

According to Minot, the egg cell at the end of its growth period is an old cell because the amount of cytoplasm in relation to the nucleus is very great. According to my criteria of senescence the egg cell is old and approaching death because the accumulation of structural material in it is so great that metabolism is reduced almost to a minimum. We know that the animal egg at the end of the growth period is almost quiescent. Warburg ('10) has shown that its oxygen requirement is very low as compared with that after fertilization. It is evident that it is capable of but little further metabolic activity. After its isolation from the body it undergoes at most only the two maturation divisions and then unless fertilized or otherwise stimulated to renewed activity it dies after a short time.

Even the maturation divisions show certain features that indicate a low rate of metabolism. In the first place they are not separated by a period of nuclear growth: apparently nuclear synthesis is impossible. And secondly, although we know little of the physiological significance of the peculiar chromatic phenomena, yet there are some indications that they too are

indicative of a low rate of metabolism. Haecker, for example has induced the appearance of paired chromosomes in somatic cells by the use of ether, and various other cases of the appearance of tetrads and heterotypic mitoses in somatic cells have been recorded, in some of which the phenomena appear to be associated with conditions which decrease metabolism. According to this view then the peculiar characteristics of the maturation divisions are connected with the physiological condition of the gamete. The stimulus to these divisions is apparently in many cases the change in environment, physiological or physical, consequent upon complete isolation from the parent body. In many other cases, however, this stimulus is apparently not sufficient to bring about maturation or its completion and this does not occur until the sperm enters the egg.

Turning now to the spermatozoon, we find that its history is different from that of the egg. Here there is no such enormous increase in volume as in the egg, but maturation divisions of the same type as in the egg occur. In the later stages of the development of the spermatozoon the cytoplasm of the sperm cell is in part used up in metabolism and in part converted into stable structural substance. The nuclear substance of the spermatozoon is evidently in a very different condition from that of the egg. The sperm nucleus is separated from the external world only by thin membranes. There is no evidence that the spermatozoon, even in a nutritive fluid, can make new cytoplasm and return to the condition of an ordinary cell. Apparently it is irrevocably committed to the function of converting other forms of energy into energy of locomotion. In short, the spermatozoon is apparently also approaching death. Its life may be prolonged by certain conditions or by quiescence for a considerable period, but sooner or later it dies unless it enters the cytoplasm of an egg.

But shall we call the spermatozoon an old or a young cell? According to Minot's criterion it must be a very young cell, since it consists very largely of nuclear material. We know but little concerning the rate of metabolism in the ripe spermatozoon as compared with earlier stages, but in all probability it is low. The energy necessary for movement is undoubtedly slight and it is not at all improbable that this energy may be furnished by

substances in the secretion or in the water which surrounds the spermatozoon. Synthesis is apparently impossible for the isolated spermatozoon: its activity is limited to one highly specialized type. Meyerhof ('11) has recently shown that in the sea urchin, *Strongylocentrotus lividus*, the respiration of a certain quantity of sperm at 19° C. decreases about thirty per cent. in four hours after removal from the body. This fact indicates at any rate that the metabolism of the spermatozoon decreases after its isolation from the body.

I believe that the spermatozoon represents an extreme case of that type of senescence which is associated, not with the accumulation of actual volume of substance but with increasing density or impermeability. In no other cell is the nuclear substance in so dense a form and certainly this condition is the most unfavorable conceivable for metabolism, and in no other cell is the cytoplasm so completely converted into stable structural elements.

If these conclusions are correct then the egg and the spermatozoon in their most highly differentiated forms represent the two extreme types of the process of senescence. Attention must, however, be called to the fact that some eggs and some spermatozoa are much more highly differentiated than others. In many of the smaller eggs increasing impermeability of the membranes may be as important a factor in senescence as the increase in actual volume. In some spermatozoa, on the other hand, considerable cytoplasm remains. But the important fact in all cases is that both gametes are highly differentiated cells and that their structural characteristics, whether these consist in accumulations of inactive substance or of impermeable membranes or of high density, have apparently reduced their metabolic activities to a minimum and made synthesis impossible. In short, both gametes appear to be in an advanced stage of senescence and both as isolated cells are approaching inevitable death. Certainly there is no indication that they consist of or contain undifferentiated germ plasm.

### 3. *The Nature and Result of Fertilization.*

In experimental reproduction resulting from the physical isolation of pieces and in asexual reproduction in nature the physical or physiological isolation of the part is usually sufficient to initiate the processes of dedifferentiation and rejuvenescence. In the case of the gametes in animals, however, differentiation of the cells has in most cases proceeded so far and the specialized structure has become so firmly fixed that physical or physiological isolation does not constitute a sufficient stimulus to initiate dedifferentiation. The maturation divisions represent perhaps an attempt of the cells to begin the process, but they are ineffective since nuclear synthesis is no longer possible and the cells continue to approach death, for the egg is unable to use its accumulated substance as a source of energy and the spermatozoon possesses no material or only a minimal amount which can serve as a source of energy.

But with the entrance of the spermatozoon into the egg conditions are at once changed. The metabolism in the resulting zygote in animals usually undergoes a rapid increase and the structural material of the egg cytoplasm, which under previously existing conditions remained inactive, now begins to enter metabolism and to serve as a source of energy. The sperm nucleus now finds itself surrounded by abundant nutritive material under such conditions that it can be used in synthesis. Moreover, as the cytoplasmic material of the egg is used up, the obstacles to metabolism become less and less and the rate of metabolism becomes higher and higher, *i. e.*, rejuvenescence proceeds at an increasingly rapid rate. In the sea urchin, as Meyerhof ('11) has recently shown, the oxidation processes are four times as great in amount in the larvæ shortly after the swimming stage is reached as in the first hour after fertilization. In those cases where the zygote forms a "resting stage," either the process of rejuvenescence goes on very slowly or else the external conditions which lead to the formation of gametes retard or inhibit the development at an early stage.

Whether the primary effect of the entrance of the sperm is a superficial cytolysis, as Loeb believes, or an increase in permeability, as R. S. Lillie and others have suggested, the result is

in general the same. Materials which under the conditions existing during the developmental history of the egg cell accumulated in the cytoplasm now become available as nutrition. During its developmental stages the egg cell was in the presence of abundant nutritive material brought to it by the activity of the parent organism and its chief activity consisted in accumulation of substance until the obstacles to metabolism resulting from this accumulation or from increasing impermeability of membranes made further metabolism impossible. At the time of fertilization external nutritive material is not present or is present only in minimal quantities, consequently, and in accordance with chemical laws, the activity of the egg, as soon as increased permeability or cytolysis has made such activity possible, consists largely in the breaking up of the previously accumulated material. It is not necessary to assume that any mysterious transformation in the nature of the egg has occurred: its activity merely changes with the presence or absence of external nutritive material. The case is not very different from that of the planarian which, in the presence of sufficient food, increases in size and accumulates material and grows old, but when starved uses up the previously accumulated material, decreases in size and becomes young, at least morphologically (Child, '11*b*). The entrance into the egg in fertilization of another nucleus, the sperm nucleus, which is in a condition somewhat similar to that of extreme starvation undoubtedly accelerates the process of dedifferentiation and rejuvenescence in the egg, but it does not necessarily have any other effect so far as the initiation of development is concerned.

Fertilization then saves both the egg and the sperm nucleus from death and initiates the process of dedifferentiation and rejuvenescence by making further metabolism possible, either in consequence of increased permeability or partial cytolysis. The evidence seems to me to point toward the conclusion that the primary influence of the sperm is an increase in permeability rather than a cytolytic action, but whichever alternative is the correct one the significance of fertilization remains the same.

As dedifferentiation proceeds and the obstacles to metabolism decrease in the egg, metabolism becomes more and more rapid.

The increased metabolic activity of the egg after fertilization has been demonstrated by various investigators and we know that the rate of cleavage increases from the early stages onward, at least up to a certain stage. During this stage of metabolic acceleration the zygote is undergoing rejuvenescence, not simply because the amount of nuclear material in proportion to cytoplasm is increasing, as Minot maintains, but because the disappearance of structural obstacles to metabolism makes more rapid metabolism possible and so permits increase of nuclear material: in other words, the increase of nuclear material is an incident or a result rather than the cause of the rejuvenescence. The increase in metabolic activity following fertilization is probably not continuous but more or less rhythmical in correspondence with the periodic changes in nuclear condition. Lyon's observations (Lyon, '04) indicate the existence of such a rhythm.

The history of the egg is in many respects similar to the history of a gland cell. During the process of loading, the gland cell is growing old and metabolism decreases until finally the loaded cell can do nothing more and is almost entirely inactive. But when the external stimulus, which corresponds to the stimulus of fertilization in the egg, reaches the gland cell rejuvenescence begins. The accumulated inactive substance becomes active, but in the case of the gland cell is simply eliminated from the cell and finally what remains of the cell is young again and capable of a new metabolic cycle.

It is an interesting speculation as to whether the egg is not after all closely related to the gland cells. If a gland cell should become isolated from the organism under conditions which render continued existence possible and if it should, in consequence of the external stimulus, undergo rejuvenescence to such an extent that it lost its special characteristics as gland cell and became more or less embryonic, it would certainly develop into a new individual in much the same manner as the egg.

In the case of the developing embryo there comes sooner or later a time probably in most cases after the young animal begins to feed, when the inactive structural products of the renewed metabolism begin to make themselves felt as obstacles to metab-

olism. From this stage on the process of senescence once more becomes apparent in the decreasing rate of metabolism. This stage where the process of accumulation of new structural substance begins to overbalance the process of removal of the old substance is undoubtedly different in different organisms, but in all cases it occurs relatively early in development and during most of its developmental history the organism is growing old.

Incidentally it may be noted that if we accept these conclusions it is quite unnecessary to regard growth as an autokatalytic process as various authors have done. The period of acceleration in growth is simply the period during which the removal of obstacles to metabolism overbalances the development of new obstacles, in other words it is the period of rejuvenescence, and the period of retardation begins when the obstacles resulting from continued metabolism become sufficient to retard the reactions; it is the period of senescence.

In certain forms with larval stages there is a second period of rejuvenescence at the time of metamorphosis, though in many cases the larval structures or some of them are too far advanced in senescence to undergo dedifferentiation and are resorbed or cast off, the further development being taken up by cells whose metabolic activity has been previously more or less completely inhibited. I believe that in general metamorphosis is the consequence of senescence of the larval structures.

To sum up: fertilization initiates the process of rejuvenescence in the egg cell and the sperm nucleus which have previously become so highly differentiated and so old in the organism of which they formed a part that physiological or physical isolation from the organism is insufficient to initiate the process of rejuvenescence. According to this view then sexual reproduction does not differ in its essential physiological characteristics from asexual reproduction or from the regulation of artificially isolated pieces. In all these cases the differentiation of the part which forms the reproductive element or system is determined by its correlation with other parts of the parent organism and reproduction is initiated by a process of dedifferentiation and rejuvenescence. In asexual and experimental reproduction the isolation of the part is usually a sufficient stimulus to initiate the

process of rejuvenescence, while in the case of the gamete a further stimulus is usually necessary.

#### 4. *Natural and Artificial Parthenogenesis.*

In some cases the development of the egg into a new organism begins at once when it is isolated from the parent organism and without fertilization. How shall we account for these cases of natural parthenogenesis? The behavior of parthenogenetic eggs forces us, I believe, to the conclusion that they are cells which, although visibly differentiated in the same direction as the true gametes, are nevertheless not so highly differentiated nor so old physiologically as eggs requiring fertilization. They resemble asexual reproductive cells or cell masses in that the stimulus resulting from physiological isolation from the parent organism is sufficient to initiate the process of dedifferentiation and rejuvenescence.

In this connection it is of interest to note that in cases where a single individual produces both parthenogenetic eggs and eggs requiring fertilization, the parthenogenetic eggs are produced earlier in the life of the parent organism than the eggs requiring fertilization. In other words, the eggs produced at earlier stages are, like other parts of the organism, not so highly differentiated nor so old physiologically as those produced in later stages. This fact of the relation of parthenogenetic and non-parthenogenetic eggs to the life cycle of the parent organism seems to me to constitute one of the strongest arguments in support of the view that the gametes are physiologically integral parts of the soma and that they differentiate and grow old in the same manner as other parts; moreover, I know of no other way of accounting for the fact.

The eggs of some species, if left for a time without fertilization, often show the beginnings of more or less normal development, but sooner or later die. Such eggs are intermediate between the true parthenogenetic and non-parthenogenetic eggs. They react to the stimulus of isolation by a slightly increased metabolism but the reaction is either insufficient to establish the processes so that they continue, or else the stimulus of isolation is not entirely adequate to initiate processes which are in all respects of normal character.



In a few cases it has also been observed that the last eggs of the breeding season show some indications of parthenogenetic development. These are doubtless eggs which have remained for a relatively long time in the ducts of the parent organism. Under these conditions the egg is cut off from its supply of nutrition, but is still under conditions more favorable to continued existence than those of the external world. As long as the egg continues to live a minimal amount of metabolism is undoubtedly going on. In the absence of external nutrition this metabolism itself must bring about a slight degree of dedifferentiation and when these eggs finally emerge from the ducts they are probably slightly younger than those extruded earlier and therefore react somewhat more strongly to the changed conditions by showing some indications of parthenogenetic development.

The work of recent years on artificial parthenogenesis has demonstrated that other means of stimulation of the egg to development may be substituted for the spermatozoon and it is, I think, sufficiently demonstrated that the essential feature of these artificial methods of stimulation lies in the fact that they make possible a continuation and increase in the metabolism of the egg. Whether they accomplish the result through superficial cytolysis or through an increase in the permeability of the membrane is not of prime importance for the present purpose: it is quite possible that some act in one way, some in the other. Certainly it does appear to be true that many of the parthenogenetic agents do increase the permeability of the membranes and if R. S. Lillie's view (Lillie, '09a, '09b, '11) that the stimulation of a cell consists essentially in increase of permeability to  $\text{CO}_2$  is correct, it is not improbable that the effect of at least many of the parthenogenetic agents on the egg is of this nature and therefore not in any sense specific. According to the view of reproduction developed in this paper, there is absolutely no reason to suppose that it is specific. Moreover, I cannot agree with Loeb ('09) that it is any more a formative stimulus than any other. It is primarily a stimulus to metabolism and the formative changes are an incident or result of continued metabolism.

But in any case the methods and agents of artificial parthenogenesis merely serve to initiate the processes of dedifferentiation

and rejuvenescence in the egg by bringing about increased metabolism. Isolated pieces of *Planaria* which are "too small," when kept at a certain temperature, to regulate into new wholes can be made to undergo such regulation by raising the temperature a few degrees and by various other methods. I believe that such cases are not fundamentally different from cases of artificial parthenogenesis.

#### 5. *Alternation of Generations in Plants and Metagenesis in Animals.*

In many of the lower plants in which sexual reproduction is known maturation is not immediately followed by fertilization, but the mature cells are spores which pass through a developmental cycle and this results in the formation of the gametophyte generation: this finally produces the gametes, which after fertilization give rise to the sporophyte. In the higher plants the gametophyte generation is much reduced and never becomes an independent, free living organism. The sporophyte produces two kinds of spores, the microspore or pollen grain and the megaspore or embryo sac. These structures in their further development represent all that remains of the gametophyte and they give rise to the gametes. In many plants then there are two reproductive cycles instead of one, although in the higher plants one of these cycles is much reduced.

The production of spores by the sporophyte is apparently associated with the senescence of this generation or of parts of it and as Klebs and others have shown can often be induced, at least after the earlier stages of the vegetative period, by conditions which decrease metabolism. But the spore resembles the parthenogenetic egg in that it reacts to the stimulus of isolation either with or without a period of quiescence by initiating a developmental cycle. It differs from the parthenogenetic egg, however, in that this developmental cycle is different from that in the course of which it arose. The spore then is not so highly differentiated or so old that it is unable to react to the stimulus of isolation by a regulatory process, but this process gives rise to an organism of different character from the preceding generation. In short, a second cycle of dedifferentiation and rejuvenescence occurs between maturation and the formation of the gametes. The dedifferentiation in this case, however, does not

carry the organism back to the original starting point. The spore, which arises from a part of the sporophyte has come to possess different capacities from the zygote and these become evident in the gametophyte into which it develops. There is certainly no reason for believing that the spore consists of or contains undifferentiated germ plasm. On the basis of such an assumption its development into a gametophyte becomes inexplicable. It seems to me that we can regard the spore only as a differentiated part of the sporophyte which in the course of regulation following its isolation from the sporophyte body does not entirely lose the physiological characteristics which it has acquired and therefore produces something different from that of which it formed a part. Moreover, in cases where apospory occurs parts of the sporophyte give rise to gametophytes without the formation of spores and in some cases regeneration in the sporophyte gives rise to gametophyte-like structures. Evidently then other parts of the sporophyte than those which normally form spores are specified in the direction of gametophytic development, but only in certain cases or under certain conditions do such parts become physiologically isolated.

In many forms also the gametophyte may reproduce asexually, giving rise to new gametophytes by various forms of budding. Here, as in the sporophyte, with every such reproduction a greater or less degree of dedifferentiation and redifferentiation undoubtedly occurs.

The existence of this type of life cycle shows very clearly that there is no immediate or necessary connection between maturation and fertilization. In these plants the maturation divisions are followed by the development of a new individual in which the cells all possess the reduced number of chromosomes. Since we know practically nothing concerning the physiological significance of the maturation process, the reason for its occurrence in connection with spore-formation is not apparent. The process seems, however, to be associated with a low rate of reaction and with conditions which prevent nuclear synthesis.

As the gametophyte becomes old it in turn gives rise to gametes, which, as in the animal are, so far as appearance goes, highly differentiated cells and if their behavior is any criterion are also

physiologically old. And here in order that anything further may occur the stimulus of fertilization is necessary.

This type of life cycle is probably connected with the great development and specialization of vegetative organs and vegetative reproduction in the plant. The sporophyte becomes so large and so highly differentiated that parts of it are physiologically or physically isolated before the stage of gamete formation is reached. These parts retain some degree of specialization during their regulation after isolation and so produce the gametophyte, which is usually much simpler morphologically than the sporophyte, but is physiologically specialized in the direction of gamete formation.

The occurrence of apogamy in the gametophytes of some species merely shows that less highly differentiated cells are capable of producing asexually the same result which in the more highly differentiated gametes occurs only after fertilization.

Alternation of generations, so-called, or more properly metagenesis, in animals is different in certain respects from alternation of generations in plants. In animals the asexual cycle always occurs before maturation and maturation and fertilization are never separated by a developmental cycle. Moreover, in animals the asexual bud which gives rise to the so-called sexual generation usually undergoes its earlier development as a specialized part of the asexual colony and becomes free if at all only when its development is advanced. Its formation is, however, undoubtedly connected with advancing differentiation and senescence in the asexual colony or in that part of it from which the sexual generation arises: in the hydroids, for example, the medusa bud very commonly arises from the most highly differentiated part of the asexual form, viz., the hydranth. It is probable, moreover, that it is initiated by the physiological isolation of a part as in other similar types of reproduction. In this respect the phenomena of metagenesis are essentially similar to those of alternation of generations in plants. In both cases there is a second reproductive and developmental cycle interpolated between the first and the formation of new gametes: in the plants this cycle occurs after maturation, in the animals before.

### 6. *Asexual and Sexual Reproduction in Relation to the Life Cycle.*

In general, where the same individual reproduces both asexually and sexually, the asexual method of reproduction is characteristic of the earlier, the sexual method of the later stages of the life cycle. In other words, when the organism is still relatively young, parts of the body which become physiologically isolated in consequence of increase in size or decreasing metabolism in dominant parts or other conditions (see p. 8) are capable of reacting to the stimulus of isolation by dedifferentiation and rejuvenescence, which is followed by a new developmental cycle.

But as the organism grows older its parts become more highly differentiated and undergo regulation less readily or not at all when isolated. At this stage of the life cycle the only form of reproduction which is still possible is reproduction by means of gametes. These parts of the organism are more highly differentiated than the asexual reproductive parts of earlier stages and, except in cases of parthenogenesis, require fertilization. In short, asexual reproduction is characteristic of the younger, less highly differentiated organism and sexual reproduction of the older, more highly differentiated. These facts constitute further strong evidence in support of the view that the gametes are really highly differentiated parts of the organism instead of undifferentiated germ plasm.

One of the most striking examples of the relation of asexual and sexual reproduction to the life cycle is found in certain medusæ belonging to the family Margelidæ. Reproduction in these forms has been described by Chun ('95) and later by Braem ('08). These medusæ reproduce asexually during the younger stages and sexually when older. Reproduction takes place by means of bud-like outgrowths which arise in a more or less definite sequence and arrangement on the manubrium, their formation beginning near the base and proceeding toward the tip. All the buds formed in the earlier stages of the life cycle are asexual and give rise to new medusæ. As the medusa grows older, however, the outgrowths continue to arise on the manubrium in the same order as before and in their earlier stages resemble the asexual buds of the younger animal, but they give rise to gonads instead of producing new medusæ asexually.

In this case then the same region of the body is concerned in both asexual and sexual reproduction and the early stages of asexual buds and of gonads are similar. The reproductive cells of the younger, less highly differentiated animal are themselves less highly differentiated and so develop asexually into new medusæ, while the reproductive cells which arise when the animal is older and more highly differentiated develop into the highly differentiated gametes, which require fertilization.

In the higher organisms, where the structural features are more stable and the capacity for dedifferentiation and rejuvenescence is limited asexual reproduction disappears and sexual reproduction remains as the only method of reproduction. In many of these forms, however, the absence of asexual reproduction in the earlier stages is due, not to the absence of capacity for reaction to isolation, *i. e.*, for regulation, but to the fact that under natural conditions parts do not become physiologically isolated. Experiment has shown, for example, that in the eggs and embryos of various vertebrates isolation of parts is followed by more or less complete regulation and the occasional occurrence of identical twins in man, as well as the occurrence of polyembryony in the armadillo as a natural phenomenon (Newman and Patterson, '09, '10), indicate that even in the mammals the earlier stages still retain a high capacity for asexual reproduction. It is not impossible that we may be able at some time with proper technique to induce asexual reproduction, even in parts of the older vertebrate organism.

In plants, likewise, sexual reproduction is characteristic of the old organism with a relatively low rate of metabolism and it can often be induced by bringing the plant under conditions which decrease metabolism. The fact that in the lower plants the gametophyte is usually simpler morphologically than the sporophyte does not, I believe, constitute a real exception to the general law. The sporophyte is a form in which most of the cells become at an early stage so highly differentiated that they are entirely excluded under ordinary conditions from the function of reproduction. Only those parts which remain in a relatively primitive condition or which differentiate relatively slowly play a part in reproduction. These parts are, so far as we can judge,

less highly differentiated than the tissues of the gametophyte from which the gametes arise. The plants therefore are no exception to the general law that asexual reproduction occurs in the less highly differentiated, younger organism or part and sexual reproduction in the older, more highly differentiated.

It has been pointed out above that the gametes are both morphologically and physiologically among the most highly differentiated cells that we know. This is exactly what might be expected if they arise as parts of old and highly differentiated organisms. Moreover, on any other basis it is very difficult to account for the differentiation of the gametes, except teleologically. A cell consisting of "undifferentiated germ plasm" is certainly capable of forming a new organism at once, provided nutritive material is accessible. Why does not the primitive germ cell use the nutritive material which comes to it for such development rather than for a series of complex differentiations which disappear as soon as the development of the new organism begins? To assert that these differentiations are connected with the necessity of fertilization is to put the cart before the horse. We know that many plants can be bred asexually for an indefinite number of generations and some have even lost the capacity for sexual reproduction or never possessed it. Moreover, recent experimental work has demonstrated that in some infusoria the supposed necessity for periodic conjugation is a myth and that under proper conditions these animals can be bred asexually for thousands of generations and perhaps indefinitely. In experiments of my own with planarians I have already bred the animals asexually for twelve generations and during this time there has been no loss of vigor and functional sexual organs have not developed at any time. It seems much more nearly in accord with the facts to conclude that fertilization is simply a necessary consequence of the differentiation of the gametes as parts of the organism, rather than to maintain that the differentiation of the gametes is a preparation for fertilization. Besides this, it is difficult if not impossible to exclude the principle of finality from the latter view. And lastly, the sexual differentiation of the gametes which is characteristic of the higher organisms is not necessary for fertilization since in many cases

where fertilization occurs it does not exist. What possible reason can there be then for this differentiation, except the reason which exists for the differentiation of any part of the soma? On the other hand, is continued metabolism without some sort of differentiation possible?

So long as we do not permit our view of the facts to be obscured or distorted by hypothesis and theory, we cannot, I believe, escape the conclusion that the gametes undergo differentiation because they form as integral physiological parts of differentiating organisms and that they are more highly differentiated than asexual reproductive cells or cell masses because they arise from older or more highly differentiated organisms than these.

Sexual reproduction is then merely the final term in the reproductive series: it is the most highly specialized type of reproduction. The gamete itself is so highly differentiated and so old that it is incapable of reproduction except with the aid of an external factor.

#### V. HEREDITY AND INHERITANCE.

If the above conclusions are correct it follows that our theories of heredity and inheritance, instead of being based solely or primarily on the phenomena of sexual reproduction, must find their basis for analysis and interpretation of these phenomena in the simpler forms of asexual and experimental reproduction. Sexual reproduction is in many respects the most unfavorable form of reproduction for investigation and analysis of the process of inheritance, for here we find the greatest number of complicating factors, viz., the high differentiation of the gametes, the presence of large masses of non-living material in the egg and the union of different gametes. We can, it is true, subject different gametes to different conditions and observe the result of their union and this method has already given results of great interest and value, but he must be an enthusiast indeed who would maintain that the complex formulæ presented by various recent investigators afford us any real insight into the actual processes of inheritance. Their terms are symbols for something, but for what we do not know and breeding experiments cannot tell us. And to say this is not to detract in any way from the interest



and value of recent work on breeding and hybridization, but is merely to state its limitations. The sexual breeding of higher animals does not and cannot at present, if ever, go much beyond the determination of empirical symbolic formulæ. We can say that the combination of  $x$  and  $y$  gives  $z$ , but all are unknown quantities and breeding experiments of this character cannot make them anything else. They do not solve the problem but merely state it in symbolic terms.

To understand, or even to formulate the processes of inheritance we must first of all know the processes in the individual and we must investigate the process of reproduction in its simplest forms. When we have done this we shall be better able to attack the problems involved in the more complex processes of sexual reproduction.

We have, I believe, in the experimental reproductions, *i. e.*, in the regulation of isolated pieces, a field of the greatest importance for the investigation of inheritance. Here we can vary the size of the reproductive element, the region of the body from which it comes, the conditions under which it shall regulate and the conditions under which the parent organism lives before the piece is isolated. And I have already shown in part (Child, '11c, '11d) and shall show further in later papers that all these factors are of importance in inheritance. Moreover the organism is primarily a dynamic system, a complex of processes, it is comparable rather to a river with its current of energy and its morphological limiting conditions (Child, '11e) than to a machine in the ordinary sense. Sooner or later we must interpret the organism in terms of dynamics rather than in terms of morphological entities. Many years ago Huxley said of the cells: "They are no more the producers of the vital phenomena than the shells scattered along the sea-beach are the instruments by which the gravitative force of the moon acts upon the ocean. Like these, the cells mark only where the vital tides have been, and how they have acted." These words, written more than a generation ago, have lost none of their value and may well serve to-day as a guide to biological investigation and a warning against certain types of biological theory.

Let us take the case of the chromosome, for example, which

plays so important a part in recent biological hypothesis. What is the chromosome? If it is what many authors seem to believe, it is an autonomous being endowed with something more than human intelligence. But if we are not willing to believe this, then we must regard the chromosome as an incident or result of dynamic processes in the organism, like other morphological entities. If this is the correct view, then it is nothing ultimate or fundamental. We must analyze it into terms of the processes which have made it and in this analysis we shall sooner or later find nothing more nor less than the whole complex of processes which constitute the organism. The organism makes the chromosomes, not the chromosomes the organism.

Montgomery ('06, p. 56) has said that we understand heredity so far as we know the behavior of chromosomes. To my mind the exact opposite of this statement is much more nearly true. The reappearance of chromosomes in successive generations of cells is itself as truly a special problem in inheritance as the reappearance of any other characteristic morphological feature of an organism, *e. g.*, the fingers of the hand, the hand itself, etc. Moreover, to state the problems of inheritance in terms of chromosomes is nothing more than a statement and not a solution of the problem, and besides this it cannot be a complete nor a correct statement.

The experimental data of recent years on heredity are very commonly regarded as supporting and confirming the germ plasm hypothesis. And particularly the at least doubtful character of much of the evidence bearing upon the inheritance of acquired somatic characters is considered as a strong indication of the independence of the germ plasm and the soma. It seems to me, however, that the real problem is obscured by our ignorance or misconception of the nature of inheritance. A very large proportion, if not most of the individually acquired somatic characters, are due to changes in metabolism which are primarily quantitative, not qualitative in character. Such quantitative changes in the dynamic processes in the organism are dependent upon actually existing internal or external environmental conditions and cannot be expected to persist indefinitely after the conditions which produced them are no longer present. As a

matter of fact, if a quantitative change in metabolism is sufficient to alter the structure to any marked degree, the effect of the change may persist in the part or parts concerned for a time or perhaps indefinitely after the conditions have ceased to act. But we cannot expect always to find characters of this sort permanently inherited, even if the germ cells are most intimately correlated physiologically with the soma, for as soon as the gametes are isolated and undergo dedifferentiation their rate of metabolism becomes very largely independent of the conditions to which they were subjected as parts of the organism. In some cases the effects of such quantitative changes may reappear to some extent for a generation or two, but they soon fade out. The non-inheritance of such characters does not then afford any evidence either for or against the independence of germ plasma and soma. In order to obtain direct evidence upon this point we must first know something of the nature of the processes which give rise to a certain character, and second, something of their correlative effect upon other parts of the body. Then we shall be able to determine what their inheritance or non-inheritance means.

It is not, I believe, too much to say that at present we have no positive evidence from the data now at hand concerning inheritance that the germ cells are independent of the soma. The established facts are simply that many individually acquired somatic characters are not inherited. We do not know, however, whether it is possible for them to be inherited even if the germ cells are integral physiological parts of the organism.

The inheritance of a character, whether it results from direct influence of factors of the external world upon the reproductive cell or cell mass or from the influence of changes in the soma, cannot depend merely upon the production of a change of any kind in the processes in the reproductive element, for many such changes disappear at once or very soon when conditions are altered. It must depend rather upon the establishment of a new dynamic equilibrium in the system and an equilibrium which is relatively stable, so that every change in conditions does not destroy it. This is doubtless the reason why so many attempts to produce mutations or new genotypes have been unsuccessful. As our knowledge of the dynamic processes in organisms increases

we shall be able to effect the establishment of such equilibria more readily.

Moreover, the apparent independence of the germ cells is readily accounted for in another way, viz., by the fact that they undergo dedifferentiation and rejuvenescence after isolation and fertilization. In this process only the most stable characteristics of the specific protoplasm acquired during their history as a part of the organism remain and all else is eliminated. Two different parts of the planarian body, for example, with different degrees and kinds of differentiation, both produce, when isolated under the usual conditions, individuals with the same general specific characters, though some minor differences connected with the different origin of the pieces may persist. There are, however, certain limits to the process of regulatory reproduction in *Planaria* and other forms and an investigation of these limits and the conditions which determine them promises results of much interest for the problem of inheritance. On the other hand, it is possible to demonstrate experimentally that changes in the hereditary capacity of parts of the planarian body can be induced by changing their position with respect to other parts. If, for example, we cut off the anterior half of the planarian body and allow a head to form at the anterior end of the posterior half, we find that the capacity of the region just posterior to the new head for developing a head when isolated is very greatly increased by its changed position in the body.

The further elaborations of the germ plasm hypothesis, the hypotheses of determinants and of unit characters as represented by discrete independent elements, are wholly unnecessary. Far from assisting us in analyzing and interpreting the phenomena of inheritance, they only complicate the problem, for if they exist they are the most remarkable entities in the world. Their assumed existence makes real progress in the solution of the problems involved almost impossible, for we can juggle with them as the facts seem to demand and there is none to say us nay, since they are beyond the limits of scientific investigation. The apparent independent variation of characters, the Mendelian phenomena, the association or coupling of characters, sex-limited inheritance and in fact all

the known phenomena of inheritance can be far more readily accounted for on the basis of different dynamic equilibria. If the organism is a dynamic system, changes in its constitution or in the conditions of the environment may alter its equilibrium and such changes may become evident, now in this character now in that or in a group of characters, according to the nature of the organism and the conditions concerned. There is absolutely no reason for supposing that a localized morphological character must be represented by a localized unit or entity of any sort. It may be and undoubtedly is simply a local manifestation of a condition pertaining to the organism as a whole. How can we doubt, for instance, that the color characteristics which have played so important a part in many Mendelian experiments are dependent upon the metabolism of the organism as a whole, rather than upon independent units existing in a hypothetical germ plasm. In the course of my own work on *Planaria* I have been able to demonstrate that the number, size and localization of such definite and sharply localized characters as the eyes are dependent upon, and vary with quantitative metabolic conditions existing in the whole organism or piece.

The germ plasm hypothesis gives us no help at any point. The facts can be more readily interpreted without it than with its aid: in fact it does not serve as a basis for analysis but merely affords us a means of paraphrasing the facts of observation into terms of absolutely unknown quantities. Why should biology continue to burden itself with this mass of speculation which affords no basis for real progress?

But if heredity is not the genetic history of the germ plasm or its determinants or unit characters, how then shall we define it? In the first place, we must admit, I believe, that wherever reproduction of any kind, whether of parts or of wholes, occurs, there we have also to do with heredity. And secondly, the facts seem to me to show that we are concerned in heredity rather with capacities, with potentialities, than with continuously existent entities. And finally, there is much evidence which indicates that these capacities and potentialities exist simply in the sum total of the dynamic processes which are

characteristic of the organism and in the colloid field in which these processes occur. It seems to me no more necessary to postulate a specific hereditary entity for a specific morphological character of an organism than it is to postulate such an entity for a sand bar or an island developing in a river.

In a recent paper (Child, '11c) I suggested a definition of heredity which I repeat here since it seems to cover the ground and does not involve unwarranted assumptions. "*Heredity is the sum total of the inherent capacities or "potences" with which a reproductive element of any kind, natural or artificial, sexual or asexual, giving rise to a whole or a part, enters upon the developmental process.*" In short the heredity of any reproductive element is simply the record in its capacities of its past history. Such a statement does not, however, imply that every factor in its past has left a permanent record. If we admit that the sex cells, like the asexual reproductive elements and the reproductive elements resulting from the artificial isolation of pieces by operation, are at some stage of their development integral physiological parts of the organism then we may define heredity as *the capacity of a physiologically or physically isolated part for regulation.*

In the realization of these capacities and potentialities environmental factors, internal and external, play an important part. A "latent" character is simply non-existent as an entity, *i. e.*, it exists only in the potentialities of the system. Latent characters are no more real things than are latent sand bars and islands in a river. The organism possesses almost infinite potentialities, but what conceivable reason is there for regarding them as different from potentialities elsewhere in nature.

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